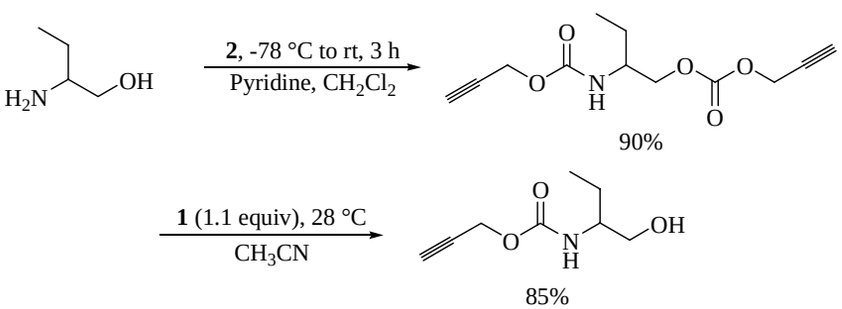
SYNOPSIS

The thesis entitled ***'Studies on the Chemistry of Carbonates and Carbamates'*** comprises of seven chapters.

Chapter 1

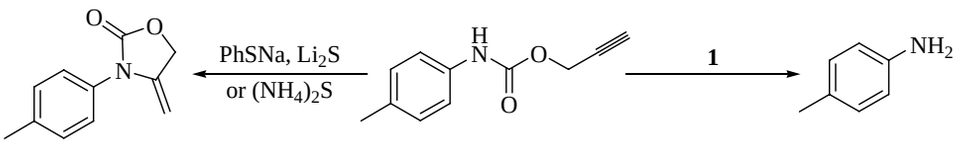
The reactivity of propargyloxycarbonyl (Poc) derivatives of amines and alcohols with various sulphur nucleophiles is addressed in this chapter. The chapter is divided into three different parts.

Part 1: The difference in reactivity of propargyloxycarbonyl (Poc) derivatives of amines and alcohols with benzyltriethylammonium tetrathiomolybdate [$(PhCH_2NEt_3)_2MoS_4$, **1**] is studied in detail and the results are discussed. It has been shown that amino alcohols can be protected as their diPoc derivatives using 2 equiv of propargyloxycarbonyl chloride (**2**). The selective deprotection of the *O*-Poc group using 1 equiv of **1** without affecting the *N*-Poc group is achieved (Scheme 1).



Scheme 1

Part 2: The reactivity of propargyloxycarbonyl derivatives of various alcohols, phenols and primary and secondary amines with benzyltriethylammonium tetrathiomolybdate (**1**) is compared with the reactivity of these Poc derivatives with other sulphur nucleophiles such as sodium thiophenoxide, lithium sulphide, hydrogen sulphide and ammonium sulphide. The study reveals that tetrathiomolybdate (**1**) is the best sulphur nucleophile for the deprotection of Poc group. Poc derivatives of primary amines cyclized to the corresponding 4-methylene-2-oxazolidinones when treated with other sulphur nucleophiles (Scheme 2).

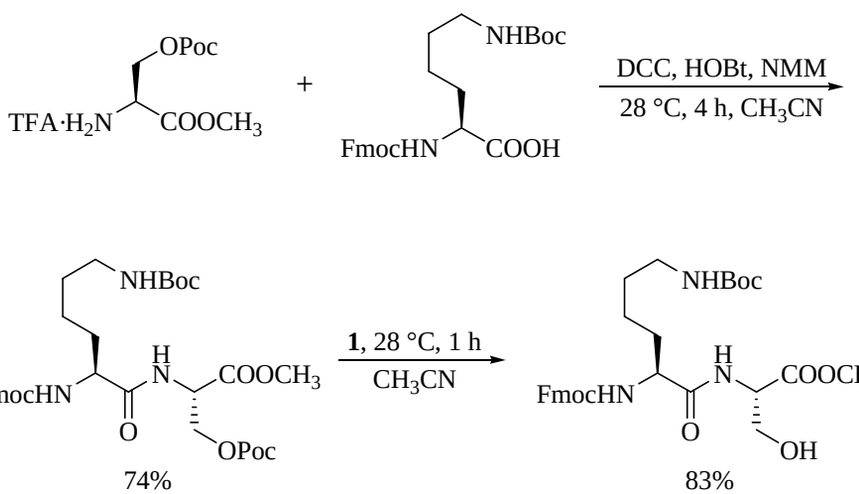


Scheme 2

Part 3: The reaction between different propargyloxycarbonyl derivatives of alcohols and benzyltriethylammonium tetrathiomolybdate (**1**) is studied. It is found that propargyloxycarbonyl derivatives can be made more reactive towards tetrathiomolybdate by substituting the propargyl system with electron withdrawing substituents.

Chapter 2

The application of propargyloxycarbonyl group for the protection of the side chain hydroxyl groups of serine, threonine and tyrosine is discussed. The *O*-Poc derivatives are shown to be stable to a variety of acidic and basic conditions and the applications of these derivatives in solution phase peptide synthesis is addressed. The easy and effective deprotection of the *O*-Poc group provides a new strategy for the synthesis of peptides bearing the hydroxy amino acid residues: serine, threonine and tyrosine.

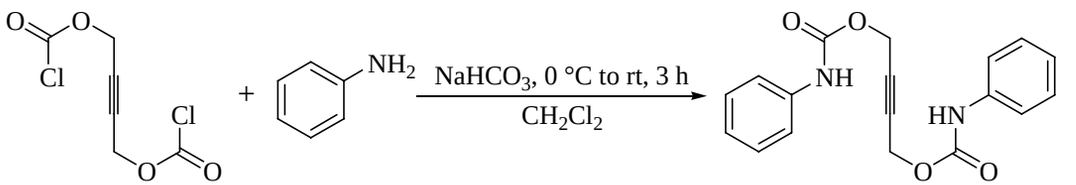


Scheme 3

Chapter 3

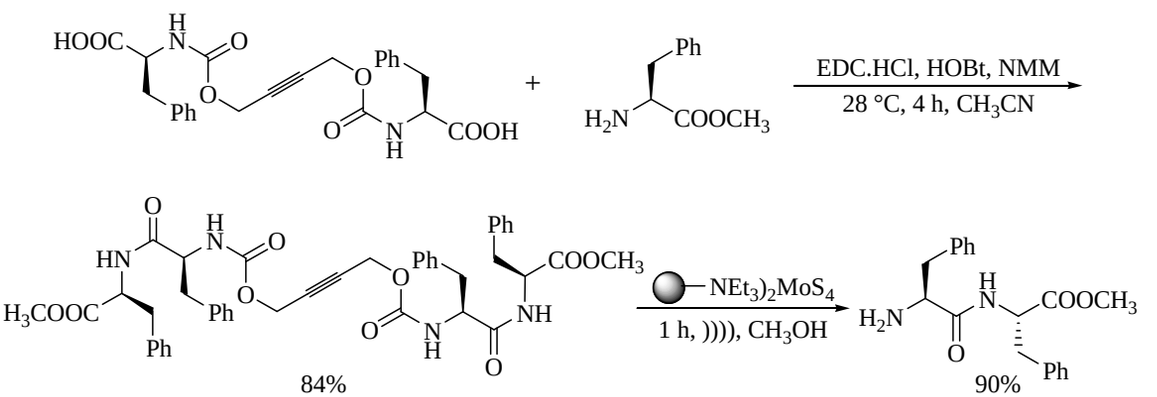
Development of a novel C_2-symmetric protecting group for amines and amino acids is described in this chapter. But-2-ynyl-1,4-bisoxycarbonyl chloride (BbcCl, **3**) is

synthesized from 1,4-dihydroxybut-2-yne and used as a reagent for protecting amines as biscarbamates (Scheme 4). These biscarbamates (Bbc derivatives) are deblocked using benzyltriethylammonium tetrathiomolybdate (**1**) to get the amines back.



Scheme 4

The orthogonal stability of the Bbc group with Boc, Cbz and Fmoc groups is established. It is also shown that Bbc group can be deblocked to the corresponding amines using resin-bound tetrathiomolybdate. The application of Bbc protected amino acids in solution phase peptide synthesis is demonstrated (Scheme 5).



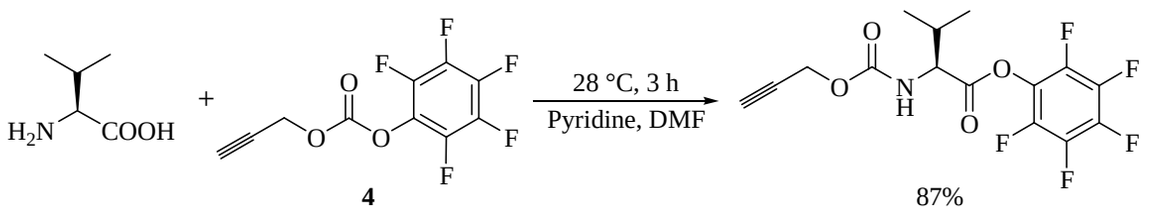
Scheme 5

Chapter 4

The simultaneous protection and activation of amino acids using various pentafluorophenyl carbonates is described in two parts.

Part 1: A very efficient and high yielding method for the simultaneous protection of the amino group and activation of carboxylic acid group using propargyl pentafluorophenyl carbonate (PocOPfp, **4**) is discussed. Treating amino acids with 2 equiv of **4** protects the

amino group as a propargyl carbamate and activates the carboxylic acid group as a pentafluorophenyl ester (Scheme 6).

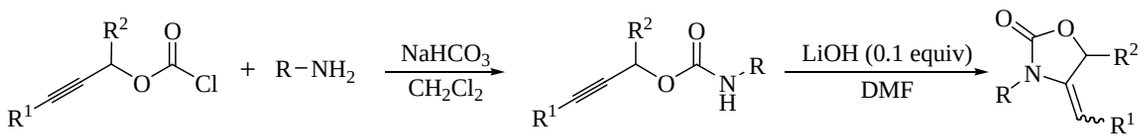


Scheme 6

Part 2: The generality of the methodology developed for the simultaneous protection and activation of amino acids using PocOPfp (**4**) is studied with five different pentafluorophenyl carbonates viz. AlocOPfp, CbzOPfp, BocOPfp, EocOPfp and TrocOPfp. The studies reveal that the effectiveness of the methodology depends on the nature of the pentafluorophenyl carbonates and on the nature of the amino acids. Sterically bulky pentafluorophenyl carbonates such as BocOPfp reacted slowly with amino acids while electron deficient pentafluorophenyl carbonates such as TrocOPfp reacted faster and gave the *N*-protected active esters in very good yields. Amino acids bearing longer aliphatic side chains reacted better than the other amino acids.

Chapter 5

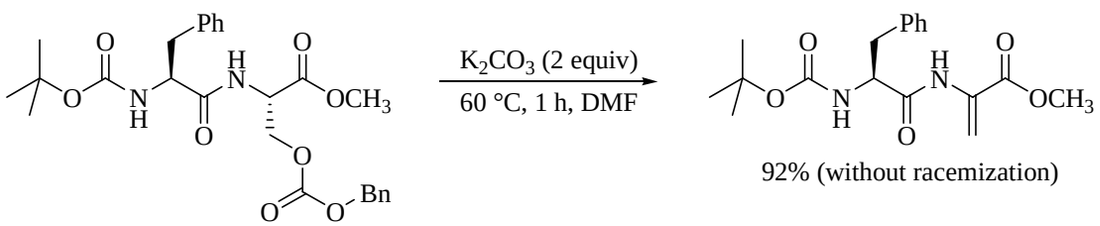
The chapter describes results of the detailed studies on the base catalyzed cyclization of *N*-alkyl and *N*-aryl-*O*-propargyl carbamates to the corresponding 4-alkylidene-2-oxazolidinones. The effect of various bases and solvents on these cyclization reactions is studied systematically to design the most suitable conditions. The best results were obtained using catalytic amount of LiOH in DMF. The cyclization reactions of *N*-aryl-*O*-propargyl carbamates were faster than the cyclization of *N*-alkyl-*O*-propargyl carbamates. The effect of substitutions on the propargyl group in these reactions is studied by preparing various substituted propargyl carbamate derivatives from the corresponding amines and propargyl chloroformates (Scheme 7).



Scheme 7

Chapter 6

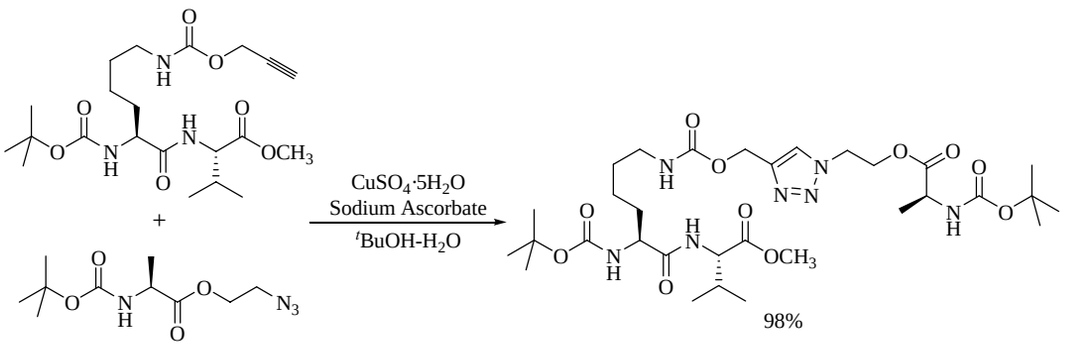
An efficient procedure for the synthesis of dehydroalanine and dehydroamino butyric acid derivatives from the preformed carbonate derivatives of serine and threonine respectively, by treating with K_2CO_3 in DMF is discussed in this chapter. The reaction proceeds stereoselectively through a *trans* E_2-elimination pathway to give only the *Z*-isomer of dehydroamino butyric acid derivatives from the carbonate derivatives of threonine. The methodology offers an easy access to dehydropeptides and proceeds without racemization of other stereogenic centers present in the peptide (Scheme 8).



Scheme 8

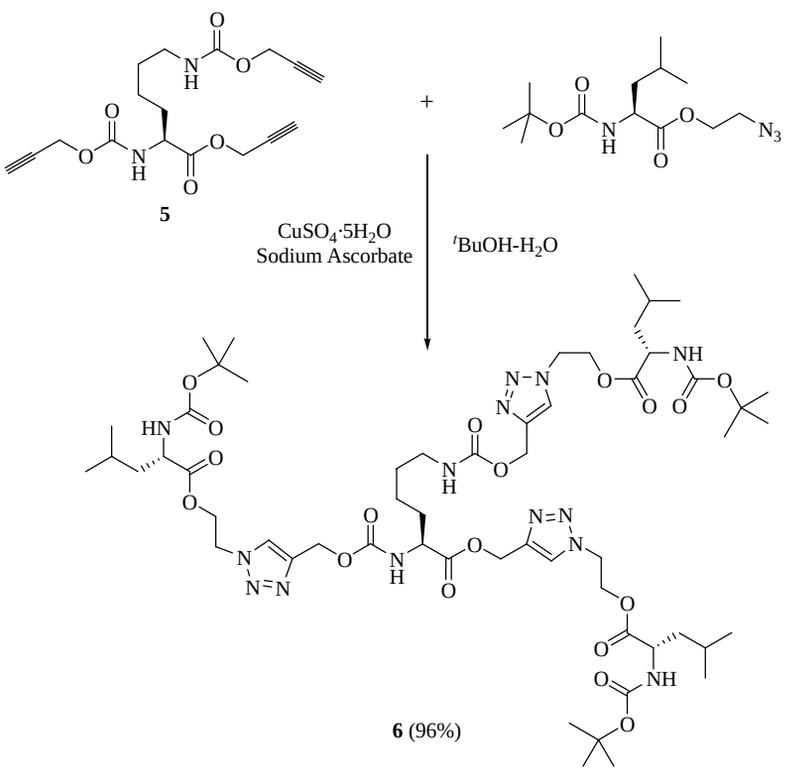
Chapter 7

This chapter describes the use of propargyloxycarbonyl derivatives of lysine as an efficient tool for the synthesis of peptide conjugates using a click chemistry approach. The Cu(I) catalyzed cycloaddition reaction between azides and alkynes is employed in the synthesis of conjugates of lysine. Peptides bearing an *Nε*-Poc Lysine residue can be synthesized using traditional strategies and these peptides can be easily conjugated with azide derivatives of sugars and amino acids (Scheme 9).



Scheme 9

The efficiency of the method is demonstrated by carrying out more than one click reaction in one pot using di and tri-propargyl derivatives of lysine. A dendritic core (**6**) is prepared from a tri-propargyl derivative (**5**) of lysine and an azide derived from leucine (Scheme 10).



Scheme 10

The abbreviations used in the thesis are consistent with those reported in *J. Org. Chem.* **2007**, *71*, 23A. Less common abbreviations are defined, the first time they are mentioned in the thesis.